Upsala J Med Sci 87: 259–267, 1982

Rapid Regression of Pituitary Tumours during Bromocriptine Treatment of Women with Hyperprolactinaemia

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ABSTRACT

Four hyperprolactinaemic women with large pituitary adenomas with suprasellar extension were given primary tumour therapy with bromocriptine. The treatment resulted in rapid tumour regression in all the women, as verified by repeated computerized tomography (CT) scans. Pronounced visual field defects were present in three of the four women before treatment. All of them had marked improvement of vision within a few days after the initiation of bromocriptine therapy and they regained normal or nearly normal visual fields during the treatment. The raised serum prolactin concentrations decreased to normal levels in all the women. Thus, medical treatment with bromocriptine can induce rapid tumour regression in patients with hyperprolactinaemia and large pituitary tumours.

INTRODUCTION

The management of patients with prolactin-secreting pituitary tumours is still controversial (4). Three main treatment alternatives are available, namely surgery, radiotherapy and medical treatment with dopamine agonists, like bromocriptine. Transsphenoidal microsurgery with selective adenomectomy has been widely used during the last few years. In patients with prolactin-secreting pituitary microadenomas, experienced neurosurgeons can produce excellent results but the cure rate decreases markedly in patients with large prolactinomas (5, 7). Radiotherapy can be given as external or internal pituitary irradiation with few immediate complications (8, 13). However, radiotherapy alone seldom normalizes hyperprolactinaemia and gonadal function within a reasonable period of time (6) and the long-term effects on endocrine function are unknown.

Here we report on results of primary bromocriptine treatment of four hyperprolactinaemic women who had large pituitary tumours with suprasellar extension. Bromocriptine induced a dramatic reduction in tumour size with rapid improvement of visual field defects.

PATIENTS AND METHODS

Four hyperprolactinaemic women with large pituitary tumours were treated with bromocriptine. None of the women had received prior pituitary tumour therapy with irradiation or surgery. Clinical details are given in the case reports and Table 1.

Prolactin in serum was measured radioimmunologically by the use of ^{125}I-labelled human prolactin and rabbit anti-human prolactin antibodies coupled to CNBr-activated ultrafine Sephadex particles (17). A prolactin preparation (VLS 3) supplied by the National Institutes of Health, Bethesda was used as a reference standard. In our laboratory the normal range for healthy women of fertile age is 2-15 µg/l (mean 6.5 µg/l) (1).

The visual fields were tested kinetically with the Goldmann perimeter and the following stimuli were used: V/4, O/4, O/3 and O/2.

Radiological examination of the sella turcica included hypocycloidal polytomography and computerized tomography (CT-scan, EMI CT 1010) with intravenous administration of iodinated contrast medium. The pituitary fossa was classified from the skull X-rays according to Thorner et al. (14), (e.g. B4: asymmetry > 3 mm with double contour throughout, B5: ballooned fossa, E: erosion).

Bromocriptine was given in doses of between 5 and 15 mg/d. During treatment the women were followed-up with repeated visual field examinations and CT-scans.

Table 1. Pituitary fossa classification and serum prolactin levels in four bromocriptine-treated women with large pituitary tumours.

	Age	Sella classification*	Prolactin, µg/l			
			Before therapy	During bromocriptine treatment 1 month	2 months	6 months
Patient 1	36	B4E	1340	67	12	14
Patient 2	56	B4E	1385	70	26	13
Patient 3	71	B5E	46	<0.5	<0.9	<0.1
Patient 4	74	B5E	5500	210	88	66

*According to Thorner et al. (14).

CASE REPORTS

Patient 1 was a 36-year-old woman with secondary amenorrhoea since 1965. She was treated with human gonadotrophins in 1968 and had an uneventful term pregnancy. Sellar X-ray was not performed. After the pregnancy she continued to have amenorrhoea. In 1971 sellar X-ray showed a slight asymmetry of the sellar floor (B2). She was then lost to follow-up. In 1980 she consulted a gynaecologist for vaginal discomfort and the long-standing amenorrhoea and galactorrhoea was noticed.

Her pretreatment serum prolactin level was 1340 μg/l. Sellar X-ray showed evidence of tumour progression since 1971 with pronounced asymmetry of the pituitary fossa and local erosion of the sellar floor (B4E). At CT-scan, there was a small suprasellar extension of a pituitary tumour but the visual acuity and the visual fields were normal.

Bromocriptine treatment (7.5 mg daily) resulted in normal prolactin levels within 2 months. At a repeat CT-scan after 4½ months of bromocriptine therapy, the suprasellar portion of the tumour was no longer visible. Regular ovulatory menstruations started after 3 months of treatment during which the patient experienced markedly increased general well-being with return of libido.

Patient 2 was a 56-year-old nullipara with 21 years of amenorrhoea-galactorrhoea. In the beginning of the amenorrhoea period she consulted several doctors but no X-ray examination of the pituitary fossa was performed. In 1980 she saw a doctor because of fear of breast cancer.

A serum prolactin level of 1385 μg/l was found. Sellar X-ray showed a large asymmetrical pituitary fossa (B4E) and CT-scan visualized a pituitary tumour with large suprasellar extension. The visual field examination showed unrestricted periphery, an absolute temporal scotoma in the right field and a relative temporal hemianopia in the left field. The visual acuity was 0.9 in the right eye and 1.0 in the left eye.

Bromocriptine was given in increasing doses up to 15 mg daily after 5 days of treatment. The visual fields improved within 6 days and were normal within 2 months. Repeat CT-scan after 2 weeks of bromocriptine treatment showed marked tumour regression but a small suprasellar portion still remained. After 2 months of treatment there were no longer any signs of suprasellar extension of the tumour (Fig. 1). The prolactin levels had decreased but were still slightly raised (Table 1).

Patient 3 was a 71-year-old nullipara with menopause at the age of 48. In 1980 she was operated with cholecystectomy because of chronic cholecystitis. Postoperatively, the patient had a period of confusion and fatigue. A 6-month history of headache and decreased visual acuity was detected. The patient was found to have hyperprolactinaemia and visual field defects and was referred for evaluation of a suspected pituitary tumour.

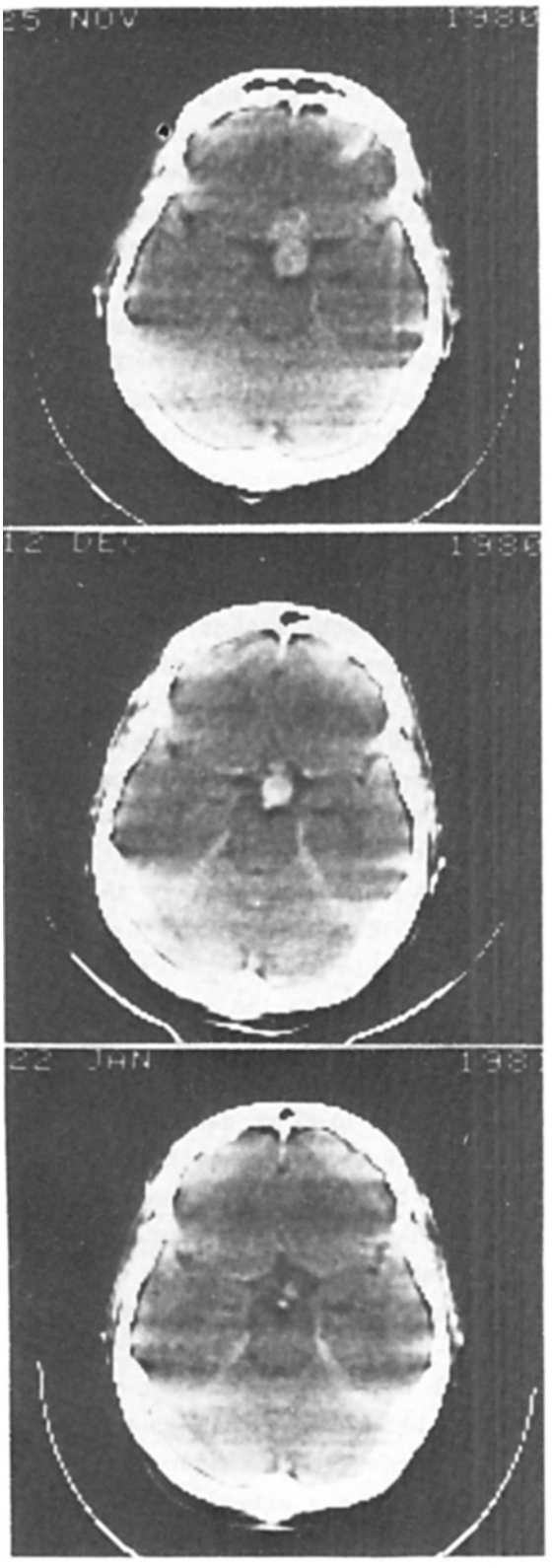

Fig. 1. Head CT-scans of a 56-year-old woman before (top) and after 2 weeks (middle) and 2 months (below) of bromocriptine treatment. After 2 months of therapy the suprasellar portion of the tumour is no longer visible.

At admittance the visual acuity was 0.7 in the right eye and 0.8 in the left eye. Visual field examination showed relative bitemporal hemianopia. Sellar X-ray showed a ballooned pituitary fossa and CT-scan revealed a pituitary tumour with large suprasellar extension. The prolactin level in serum was 46 µg/l (Table 1).

Bromocriptine therapy (7.5 mg daily) normalized the raised serum prolactin concentration within one week. Some improvement of the visual fields was recorded after one week and after 6 weeks of treatment the improvement was marked with visual acuity of 0.9 in the right and 1.0 in the left eye. After four and a half months the left visual field appeared normal and the right field had further improved. Evidence of rapid tumour regression was also found at the radiological examination. A CT-scan after 6 weeks of treatment showed regression of the suprasellar extension and after 8 months of therapy only a small suprasellar tumour portion was visible. During the bromocriptine treatment the patient reported loss of headache and a pronounced increase of general well-being.

Patient 4 was a 74-year-old woman with 2 term pregnancies and regular menstruations until the age of 48. She had been treated with prednisolone (5 mg daily) for one year because of polymyalgia rheumatica. The patient was admitted to the hospital with a 6-month history of visual deterioration.

The visual acuity was 0.8 in the right and 0.1 in the left eye. She had almost complete temporal hemianopia in the right field. Left visual field examination showed complete temporal hemianopia and poor vision in the nasal field. X-ray showed enlargement of the pituitary fossa with destruction of the sellar floor and the dorsum sellae and CT-scan revealed a large suprasellar extension of the pituitary tumour. The prolactin concentration in serum was 5700 µg/l. Transnasal aspiration biopsy confirmed the diagnosis of a pituitary adenoma. The tumour was classified as an invasive pituitary adenoma (9).

Bromocriptine therapy (5 mg daily) resulted in a rapid decrease of the high serum prolactin concentration but the prolactin level was still slightly raised after 6 months of treatment (Table 1). During the bromocriptine therapy, a rapid improvement of the visual acuity and visual field defects was recorded. After two weeks of treatment the visual acuity was 1.0 in both eyes and only small bitemporal defects remained. Three and a half months later the left visual field appeared normal (Fig. 2). Repeat CT-scan after 5 weeks of therapy showed regression of the suprasellar tumour. After 7 months of bromocriptine treatment only a minor suprasellar portion remained. During the treatment the patient experienced a marked increase in well-being.

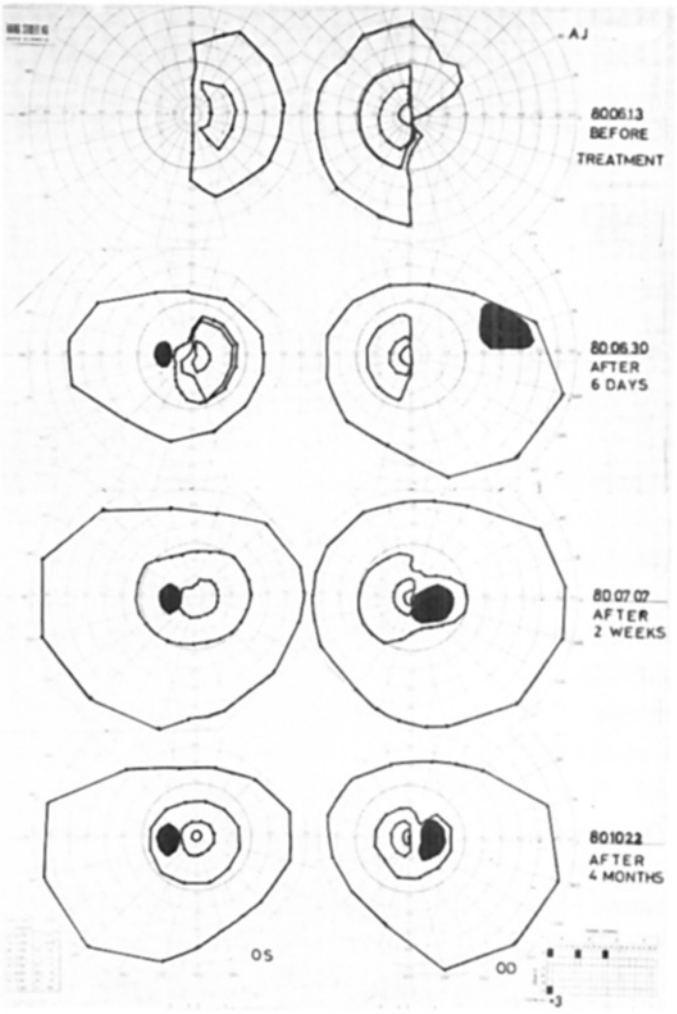

Fig. 2. Visual fields of a 74-year-old woman before and after 1, 2 and 16 weeks of bromocriptine therapy. The bitemporal hemianopsia rapidly improved during the treatment.

DISCUSSION

Medical treatment with bromocriptine resulted in tumour regression in our four hyperprolactinaemic patients who had large pituitary tumours with suprasellar extension. Three of the women had visual field defects which rapidly disappeared or markedly improved during the treatment. Repeated CT-scans showed regression of the suprasellar extension of the tumours in all four women. The rapidity of the tumour shrinkage was remarkable in three of the patients. Radiologically demonstrable tumour regression was evident after only 2-6 weeks of bromocriptine treatment. The daily dose of bromocriptine

was only 5-7.5 mg in three of the four women. The improvement of the visual fields was observed even earlier, being obvious after only a few days of treatment. The results agree well with those of other recent studies in which bromocriptine-induced regression of pituitary tumours has been objectively verified by repeated CT-scans or contrast radiology (2,3,10,11,12,15,16,18).

The prolactin levels before treatment was very high in three of our patients. One woman (patient 3) had moderate hyperprolactinaemia (46 µg/l) before treatment despite evidence of a large pituitary tumour with suprasellar extension. It can be questioned if she had a prolactinoma. The prolactin hypersecretion may be caused by disturbed production or transportation of the prolactin-inhibiting factor (PIF) because of pressure from a large non-functional adenoma. It is interesting that bromocriptine had a regressing effect also on this tumour. Wollesen et al. (18) recently showed that bromocriptine was effective in reducing the size of not only prolactin secreting but also nonsecreting extrasellar pituitary tumours.

Transsphenoidal adenomectomy has frequently been recommended for treatment of hyperprolactinaemic patients with evidence of pituitary tumours. However, surgical treatment of large prolactinomas is associated with poor results (5, 7). Medical treatment with dopamine agonists like bromocriptine is well tolerated and has no serious side-effects. This and other recent clinical studies have demonstrated that bromocriptine can have a remarkably rapid tumour-regressing effect on large pituitary adenomas. It is therefore worthwhile to start with bromocriptine treatment even if surgery is planned. The likelihood is great that the tumour will decrease in size and become more easy to remove surgically later. Our results like those of other recent studies strongly suggest that bromocriptine is the primary treatment alternative in patients with large prolactinomas.

ACKNOWLEDGMENTS

The study was supported by the Swedish Medical Research Council (Grant No 13X-3145). We thank Mrs Birgitta Bohman for excellent secreterial assistance.

REFERENCES

1. Bergh, T., Nillius, S.J. and Wide, L.: Bromocriptine treatment of 42 hyperprolactinaemic women with secondary amenorrhoea. Acta endocrinol 88: 435-451, 1978.
2. Chiodini, P., Luizzi, A., Cozzi, R., Verde, G., Oppizzi, G., Dallabonzana, D., Spelta, B., Silvestrini, F., Borghi, G., Luccarelli, G., Rainier, E. and Horowski, R.: Size reduction of macroprolactinomas

by bromocriptine or lisuride treatment. J Clin Endocrinol Metab 53:737-743, 1981.

3. Corenblum, B. and Hanley, D.A.: Bromocriptine reduction of prolactinoma size. Fertil Steril 36:716-719, 1981.
4. Edwards, C.R.W. and Feek, C.M.: Prolactinoma: a question of rational treatment. Br Med J 283:1561-1562, 1981.
5. Fahlbusch, R.: Surgical failures in prolactinomas. In: Pituitary Adenomas. Biology, Physiopathology and Treatment (eds. P.J. Derome, C.P. Jedynak & F. Peillon), pp. 273-284.Asclepios Publishers, France, 1980.
6. Gomez, F., Reyes, F.I. and Faiman, C.: Nonpuerperal galactorrhea and hyperprolactinemia. Clinical findings, endocrine features and therapeutic responses in 56 cases. Am J Med 62:648-660, 1977.
7. Hardy, J.: Transsphenoidal microsurgical treatment of hypersecreting pituitary adenomas. In: Endocrinology 1980 (eds. I.A. Cumming, J.W. Funder & F.A.O. Mendelsohn), pp. 715-722. Australian Academy of Science, Canberra, 1980.
8. Kelly, W.F., Doyle, F.H., Mashiter, K., Banks, L.M., Gordon and H., Joplin, G.F.: Pregnancies in women with hyperprolactinaemia: Clinical course and obstetric complications of 41 pregnancies in 27 women. Br J Obstet Gynaecol 86:698-705, 1979.
9. Lundberg, P.O., Drettner, B., Hemminsson, A., Stenkvist, B. and Wide, L.: The invasive pituitary adenoma. A prolactin-producing tumor. Arch Neurol 34:742-749, 1977.
10. McGregor, A.M., Scanlon, M.F., Hall, R. and Hall, K.: Effects of bromocriptine on pituitary tumour size. Br Med J 2:700-703, 1979.
11. Prescott, R.W.G., Johnston, D.G., Kendall-Taylor, P., Crombie, A., Hall, K., McGregor, A. and Hall, R.: Hyperprolactinaemia in men - response to bromocriptine therapy. Lancet I: 245-248, 1982.
12. Spark, R.F., Baker, R., Bienfang, D.C. and Bergland, R.: Bromocriptine reduces pituitary tumor size and hypersecretion. Requiem for pituitary surgery? JAMA 247: 311-316, 1982.
13. Thorner, M.O., Besser, G.M., Jones, A., Dacie, J. and Jones, A.E.: Bromocriptine treatment of female infertility: report of 13 pregnancies. Br Med J 4: 694-697, 1975.
14. Thorner, M.O., Edwards, C.R.W., Charlesworth, M., Dacie, J.E., Moult, P.J.A., Rees, L.H., Jones, A.E. and Besser, G.M.: Pregnancy in patients presenting with hyperprolactinaemia. Br Med J 2: 771-774,1979.
15. Thorner, M.O., Martin, W.H., Rogol, A.D., Morris, J.L., Perryman, R.L., Conway, B.P., Howards, S.S., Wolfman, M.G. and MacLeod,

R.M.: Rapid regression of pituitary prolactinomas during bromocriptine treatment. J Clin Endocrinol Metab 51: 438-445, 1980.

16. Wass, J.A.H., Williams, J., Charlesworth, M., Kingsley, D.P.E., Halliday, A.M., Doniach, I., Rees, L.H., McDonald, W.I. and Besser, G.M.: Bromocriptine in management of large pituitary tumours. Br Med J 284: 1908-1911, 1982.
17. Wide, L.: Use of particulate immunosorbents in radioimmunoassay. In: Immunochemical Techniques, Vol. B. (eds. H. van Nunakis & J.J. Langone) Vol. 73 of Methods in Enzymology (eds. S.P. Colowick & S.P. Kaplan) pp. 204-224. Academic Press, New York, 1981.
18. Wollesen, F., Andersen, T. and Karle, A.: Size reduction of extrasellar pituitary tumors during bromocriptine treatment. Ann Int Med 96: 281-286, 1982.

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